Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

Roundtable Discussion

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DR. WAGNER:

We appreciate you all hanging around for a roundtable. We have found these to be, uh, uh, very helpful, uh, although they tend to be extremely wide ranging and, uh, and I'm concerned that there isn't – we try – in order to keep them from just going, spinning immediately out of control, we try to, uh, pose a framing question. It's very hard to pose a framing question for this one but, maybe we can start with something like this.

Reminding you that the charge our commission has, um, we have understood to be twofold. One is the very specific question about about the anthrax and preparation for medical countermeasures for anthrax, the vaccine itself, the AVA vaccine. And the second is imagining that the anthrax question really just helps us focus on the whole much larger issue of medical countermeasures, uh, for children and the conditions under which we should recommend, um, for those going forward.

Maybe I'll let you pick one or the other as we go around but, what do you imagine to be the specific point which you would encourage the commission to pivot it's decision on or to help resolve? Uh, and either the narrower question or the larger question.

As I said I don't think that's going to narrow things down terribly, (laughter) terribly much. Who might want to start with that and we'll just rundown the – Yes, go for it, please.

MR. LOCKWOOD: Sorry. It's a little cool outside.

Um, I would say that if you look back at the planning we've done, uh, the issue is that, and it shouldn't be about money but, we have spent billions with a B and preparing literally for the mass dispensing of antibiotics. The missing piece, not only for children but, in the broader spectrum is, um, we are not planning as part of our mass dispensing, at least not that I'm aware of, to incorporate into that mass dispensing plan, the vaccine. If the vaccine is to be a part of it, then we need to look at how we're tooling ourselves right now for the delivery of medical countermeasures as a whole because as I said before, as you're delivering the antivirals, the issue is most of us are building off of a head of household type delivery system, and as soon as you add the vaccine, it changes everything.

It now makes it so that it's evasive. Individuals have to be there to receive the vaccine. So, I think that the, the current systems in place, while I think that they are based on sound planning procedures that as we've gone through this process, we're learning more and more that the gap is the vaccine, and currently it's not approved for post-use without the Emergency Use Authorization, and then, they investigate it for children.

DR. WAGNER: So, so, your last phrase kind of took us in another direction but, the point, Mr. Lockwood, I think I heard is independent of whether or not there is, uh, or what degree of pre-event activity might take place, you would say we are going to need to pay attention either way to the delivery system issues.

MR. LOCKWOOD: Correct, but my point about mentioning the last part was that in itself complicates our delivery. The, the need to have that, the timeline to do it, that process, it's got to be a part of the process, as a whole. We have to know that all going into it.

DR. WAGNER: Alan.

DR. FLEISCHMAN: Having read what the Secretary asked this commission to do, and having listened to the very broad, um, concerns that people have raised, my counsel would be to remember the word children in everything you write and do and, and advise and research, and to narrow the focus so that your report will be most effective in creating a decision or change. Rather than having broad kind of counsel about there's a lot of problem that somebody's got to fix. So, I would counsel as carefully as you can to focus on children, research and anthrax vaccine, um, and make recommendations regarding those, which will probably end up with your being very effective.

DR. WAGNER: Don't kick the can down the road is what you're saying. Suzet.

DR. MCKINNEY: Hi. You know, as I think about this issue and, um, the comments that Mr. Lockwood made, I guess in my own practice, I'm not so much concerned with whether the medication or the countermeasure is a vaccine or an oral antibiotic. I think over the years that we've been doing this work certainly in my ten years of doing this work, I've seen what I now coin as the "disaster du jour". So, we've gone from 9-11 and anthrax to smallpox and SARS, to Hurricane Katrina, to floods and earthquakes and hurricanes. And so, at least in my practice, we've become accustomed to this, you know, what people generically refer to as "all hazards" approach.

I think the recommendation that I would make goes back to something that I said earlier but, also something, um, that I believe I heard Dr. Benjamin reference this morning, and that is the whole of community approach because the response and the success of any vaccination campaign will be, all of the interested stakeholders having involvement, having input and assisting in the delivery of those medical countermeasures.

Um, it may not be your public health officials or, it would be your public health officials providing vaccination but, I think, those vaccination efforts, um, could also be equal to or community level efforts such as, uh, community based organizations and faith based organizations assisting in the education and the partnerships with public health and the healthcare sector will be just as important. So, that would be my recommendation to include that whole of community approach.

DR. WAGNER: The whole community approach. Thank you. Dr. Rasmussen.

DR. RASMUSSEN: I think, um, we're on a theme a little bit here. Um, I think one of the keys is trying to understand what families, what do parents already know about the risks? What can we – how can we best explain to them what the risks that they're facing, and then, what the benefits of the vaccine would potentially be? And, um trying to get some information on those opinions even before, uh, a trial would be done, I think would be helpful.

So, so, we know what people know. Know what they need to know. Know who they might trust in an event, who they would listen to, um, and so we know who the key partners for public health need to be in that sort of situation.

DR. WAGNER: Education of family and communities.

DR. RASMUSSEN: Yeah, and knowing what they know at the start and getting input from them about that.

DR. WAGNER: Ah, okay, got it.

DR. MARSHALL: So, I suppose I would say perhaps a central challenge to you all to think about is the, your framework and how you're going to sort of justify that in terms of moral norms and we talked a little bit about –

DR. WAGNER: I'm sorry, justify in terms of --?

DR. MARSHALL: Your framework and how you're going to justify it in terms of, you know moral norms or moral theory.

DR. WAGNER: Moral norms --.

DR. MARSHALL: So, uh, we talked about Paul Ramsey this morning. Talked about, talked about Kant. So, I think that there's a challenge to perhaps where you were proceeding and that that's going to take some conversation and some thought.

DR. WAGNER: In the past, in past reports, we've drawn upon a fairly, uh, specific list of principles. Is that the sort of thing you're challenging us to, to have here?

DR. MARSHALL: Well, I guess I'm sort…principles, but what informs those principles?

DR. WAGNER: Um-hmm. Okay. Got it. You're not making it easier, though. Okay, Capt. Maher.

CAPT MAHER: And, I don't know if I'm going to be able to make it any easier myself either but, um, I echo what, what my colleagues here have said and, and I would recommend that all the different topics and points that have been brought out at this meeting be very carefully considered and weighed. Um, taking a holistic approach. Looking at what we know. What we don't know. Um, if we were to do a study pre-event, how would that be done? What would it inform? Is it going to inform what we're assuming it's going to inform? Um, the assumptions about how we intend to respond and whether or not those are sound assumptions.

I think there is a very key point to understanding what the real acceptability on behalf of the public for this particular vaccine in children is going to be. We're making a lot of assumptions that parents may or may not accept the vaccine based on similar but unrelated experiences. Um, and challenging a lot of those assumptions and the assumptions that you might be able to get the information in the middle of the emergency.

We'd love to think that we can plan and we are planning to develop and have protocols ready to go during the response but, again, there's a lot of underlying assumptions that I think need to be really, carefully looked at.

DR. WAGNER: And, Dr. Benjamin.

DR. BENJAMIN: You know, we're in a very rapidly changing world, um, with an amazing amount of new threats both from nature and from people. We're also in a new world in which our science, um, may very well get ahead of us but, at least, right now, we have an amazing amount of science.

We're, we're getting ready to decide whether or not we can give a drug to a particular individual based on their genetic structure. Right? We can look at both them and the drug and say, it might work.

DR. WAGNER: Yeah, personalized medicine.

DR. BENJAMIN: Very much personalized medicine, um, and our framework for thinking about that particularly in a research environment is old school. And, I think we need to begin thinking in a new way, recognizing, um, that, of course, adults will lead that way, um, but we have historically left children behind, even in our current research approach, and I think that we need to stop doing that. Um, I think that, um, children have certainly demonstrated over the years, they're not little adults, um, both physiologically and the fact that they're growing and rapidly changing. And, if we don't build a research model, which encompasses them in this rapidly changing world of both threats and opportunities, I think we will miss the boat.

DR. WAGNER: Let me, um – I won't do that yet. Well, maybe I will do it, very, very quickly. Uh, um, the kind of studies we're talking, we've been talking about Capt. Maher have been around dose response. Um, to the extent that this is relevant or even if it's not can you

imagine that you yourselves, knowing what you know, as experts in these areas would enroll your children in such a study?

CAPT MAHER: I have to say I've asked myself that question having been involved in research for many, many years. Prior to coming to FDA, I was involved in, um, HIV/AIDS clinical trials. And then, at DMID, I was involved in a lot of the influenza trials. And, from, from my mother perspective of what I considered back then, yeah there were certain trials I would enroll my child in, and it really depended on how comfortable I was with the information about the trial. How much confidence and how much I really understood what the trial was about, what the risk to the child was and what the benefit to my child might be.

Um, with regard to the anthrax vaccine, I'm not in a situation to have to opine on that now. So, I guess it's, it's, um –

DR. WAGNER: And, I wouldn't want to force you to, that's not – please, don't feel forced to answer this question.

CAPT MAHER: But, my judgment would still be based even as an adult, my judgment would be based on understanding and having as much information as possible to understand the decision that I'm making and why I'm making it and what the benefit might be, not just to myself but, in the long-term.

DR. WAGNER: Lonnie.

MS. ALI: I just want to ask you as a follow-up to that would you enroll your child into uh, a study where there was above minimal risk, where there was no really direct benefit to the child, speaking from your mother perspective?

CAPT MAHER: Yes, depending on the study I would and depending on the age of my child at the time, and what they thought because I would take into account, you know, what they thought but, I wouldn't say no.

DR. WAGNER: Alan had his hand in the air.

DR. FLEISCHMAN: In 20 years of clinical practice in neonatology, large numbers of families would ask me if this were your child, what would you do? And, I always told them that was the wrong question. It's their values. It's their history. It's their family. It's their decision. But, most importantly, if I said I would withdraw treatment and allow this child to die or I would do this heart transplant or whatever else it was, then that family knowing that will believe that if they don't have the same view as I do that I think less of them. So, I have never answered the

question that many doctors answer and that is what would you do it if was your mother or your child.

Um, but what the family is really asking you, do you believe this is reasonable for a family to do? And, my response to you would be, yes I do believe it is reasonable for a family to do, but that it isn't going to be the majority of families that's going to do it. So, our job is to make sure that the information that they receive is fair and transparent and real and for those families who don't wish to do it, applaud them because they've considered it. And, for those families who do, applaud them because they've done it.

DR. WAGNER: Dan. Thank you.

DR. SULMASY: Yeah, the question I was going to ask is a variant on, uh, Jim's question, which will get everybody off the hook, um, but, also, avoid the kinds of concerns that Dr. Fleischman just raised, uh, and it's, it's sort of a question that Lonnie you had asked in one of our calls, uh, which is, you know, why would a parent ever be justified in enrolling a child in such a study. Um, and I think that, that way you don't have to answer it for yourself but, what kind of reasons would be reasonable reasons from an ethical point of view for a parent to enroll a child? And, maybe ask more than one person too.

DR. WAGNER: Let's go to Mr. Lockwood, first.

MR. LOCKWOOD: So, as I said earlier today, um, if an individual is in a position where they feel they're at risk, and they believe that they will get the anthrax vaccine, if there's a threat that they believe they can also then infect their family, I think that that is one of those areas where, um, an individual may make the decision that it's appropriate for them to do that, um, but as I did say this morning, and I think I already heard echoed is it is an individual, personal family decision that will be made. The employer won't make it for them. It should be voluntary but, it should be available to them if they want to.

DR. FLEISCHMAN: My argument, Dan, would be the questions really two things. One, um, is the risk minimal enough but greater than, you know, minor increase over minimal. Um, but, many families wish their children to behave in ways that show that they care for the community. In Thanksgiving, my grandchildren go and give meals to homeless people. Um, and that's not something. They'd prefer to go to the, uh, Macy's Parade but, they understand and they feel good about it and we talk about at the end of the day. So, there are many families who really believe their children should learn early on about altruistic giving back to the community for other children in the future, even though it might hurt a little bit. And, I think that's laudable and appropriate and ought to be applauded.

DR. MARSHALL: Um, so, I would say, um, that there are those in the research ethics community who make the argument, I don't ascribe to it that, at least adults have a moral obligation to participate in research and that we all do, as members of a community. Um, I, I, don't go that far but, I think one thing that you heard today has to do with infrastructure and that would be a reason. So, thinking about your role and your responsibility just to the community, if you're part of the infrastructure that's going to support a response, uh, then that's something that you would consider or should consider ahead of time, or you perhaps shouldn't be in that role.

I mean that does beg the question of voluntariness once the event happens but, there should be prospective thought at the level of the individual about that and her or his family.

DR: FARAHANY: I may be misreading some of your responses but, I – it seems to me like generally, uh, the group of you before us today are favorable of a pre-event study under certain conditions. Um, and if that's true, uh, then I have a couple of questions. One is what kind of information would you hope to learn from that study? Um, and related to that, how do you expect the information that we might learn from such a study would change a post-event response by having that information? So, what do you hope to learn and how do you expect that it'll impact our post-event strategy or response?

DR. MARSHALL: So, have a -- this is based perhaps on experience with the H1N1 pandemic in Minnesota and actually thinking about working with the state department of health on pandemic planning prior to H1N1, um, and that is the importance of community engagement. It took the two groups that were charged by the state department of health, um, two years to, you know, come up with a framework and a plan and the first part of that was really robust community engagement of, you know, over 120 people in the room representing, you know, the attorneys for persons with disabilities, um, all, you know, Native Americans in Minnesota.

So, all of the stakeholder communities, I mean that's obvious and it's been mentioned before but, then, you know, importantly focus groups. And, I'll have to echo that we found what you found earlier and that was a lot of groups that are historically, um, sort of disadvantaged during a pandemic, um, said the same thing to us that you said. You know, nobody, you know, people come to us quite frequently. Um, we're perhaps an over researched community but, we don't have the sense that you're listening. And as the H1N1 pandemic played out in Minnesota, there was this same pattern that you saw in 1918 and, you know, and prior to that and that is people who were socially disadvantaged had a greater impact. And there was greater mortality and morbidity among the Native American community, among rural and urban poor, among certain rural communities.

Um, and it, um, I'm being inarticulate here but, I guess I can't impress upon you enough the importance of doing community based engagement and that that in and of itself is research. So, maybe you're thinking about the wrong protocol here or maybe you need to be thinking about additional protocols that have to do with social science research on community engagement.

DR. RASMUSSEN: Well, I think we would hope to learn what the right dose is, and then, whether you're going to get with that dose an immune response that's protective.

I think the other thing, at least from our experience with H1N1 and the vaccine was it was really helpful to be able to say when people were saying this is a totally untested vaccine, you're experimenting on the US population, to be able to say, "No that's not true. We use this same vaccine every year. It's made exactly the same way. It just has a different cassette in there for the H1N1 virus." And, I think it would be really hard to convince people to get, to give their children a vaccine that you can say had never been tested in children, at all. I think, um, just knowing the, the, um, constant calls we got during the pandemic and questions that we got daily from clinicians, as well as, uh, the general public.

DR. WAGNER: Those data may not be available, right? I mean, we don't even know in the adults what the immune protection level is, right? So, carry that out. If I know ahead of time – I can't answer that for you. Does that change your –-

DR. FARAHANY: Would safety data be enough. Right? I mean, if it is dosing, it gives us some level.

DR. WAGNER: We could get an immune response but, we don't know if that's immune protection.

DR. RASMUSSEN: Yes, immune response that's expected to be protective. I mean, I think we have a sense of what is expected to be protective.

DR. WAGNER : A surrogate marker, right?

DR. KUCHERLAPATI: That's a surrogate marker, yes.

DR. WAGNER: A surrogate marker.

DR. RASMUSSEN: I think we, I think that is – we use that for a lot of things.

DR. KUCHERLAPATI: Well, I think that just to comment – my microphone is on. Just to comment and I have two comments, just general discussion.

First, of all, as to whether or not we get adequate amount of information from this that may be true but, you have to have this experiment done before you can do other things. Right? So, it's a sort of a moot question. So, if you cannot do this, you cannot do any other, anything further to expand on the knowledge that you'll be able to obtain. So, uh –

And, the second point is indeed that, you know, immune response is a well-established surrogate for, as to whether or not that's going to be effective. Not, absolute but that's the best that you can have. You cannot infect these people.

DR. MICHAEL: Just to make a technical point that's not completely true. I mean, I mean, we just studied – we just published a pretty extensive analysis of a vaccine study in Thailand which showed some degree of efficacy and to really identify a correlative risk of infection requires an enormous amount of science, and usually that's not done in vaccine development. It just – you have something, you can measure a general immune response and, in general that correlates with efficacy. It's not the same as saying this is the correlate. I think this is important in pediatric studies because even though you could look at those same immune responses, you may not be measuring the right thing. And so, by dropping the dose, you may see these other measurable but, not relevant, you know, theoretically not relevant immune response, and they still look good but that what you're really interested in, you're not looking at. And, that's, I think some of the danger of, of, of doing these dilution studies, when you haven't truly nailed the correlate.

CAPT MAHER: I think to the extent that under the right circumstances, the right questions can be asked and the rightly developed protocol. It would actually help the response on the backend because it can, at the very least inform what we're going to be looking for. We can target what type of information do we need to get out of the response that the product is being used, and it could also inform clinical guidance of the product.

DR. MICHAEL: So, sorry to keep on harping on this one point but, um, getting back to the whole community concept that, um, that Dr. McKinney has mentioned now several times, do you think it's, it's going to be possible to do a proper bioethically robust study in a post-event environment? When you have all these issues swirling about the vaccine has never been tested in children. We're not really sure even in adults what really is the right level of immunogenicity. All of these questions. Is that going to be, um -- Let me – Do you think it can be fairly done?

DR. MCKINNEY: I think when you talk about the issue of vaccines in children, whether it's the AVA vaccine or any other vaccine, there are always going to be questions and issues and primarily concerns from parents. Um, just a couple of weeks ago, I found myself in a situation having a discussion with a parent about HPV vaccine, in a setting where I was not intending to have that discussion.

Um, but here is a vaccine that not only has been tested and approved but, is now recommended for children but, yet, there are still people among our general public despite all the information that's available now, who say that's a new vaccine. It hasn't been fully tested yet. So, I think, um, from my perspective, I think we have to start somewhere, and I think we have to

do what we can. Um, I don't think there is a way to do this where we're going to please everyone but, we do have to make any and all efforts to gather information.

I agree with my colleague that, um, social science can also be considered, um, as a part of research. Um, so I think we have to start where we can and do what we can to gain as much information. There will be parents out there who arguably will be concerned but, we'll be able to take in information and understand that information and educate themselves. On the flipside, there will be just that many people, if not more, who won't do the same.

DR. WAGNER: Sorry, broke my own rule. Uh, you've been talking all to, uh, to the issue of pre-event testing. Okay. Dr. Fleischman and then Dr. Marshall.

DR. FLEISCHMAN: Yeah, I, I think that we can construct a post-event, robust research agenda with those families who do accept the immunization and those who do not. That we create an infrastructure. We fund it in some kind of, you know, escrow account. Um, we, um figure out exactly what the questions are we want to ask. I think we can go into the depth of the immunogenicity work that you would recommend. I think we can go into the social science work, as to why families refuse. They might come back tomorrow and ask for it, and we want to know that.

We could do this electronically. We could do this with cell phone technology. We can do things that we're doing internationally to collect data from large populations in the HIV world. Um, so, I see no reason at all that a pre-event study precludes anything about a post-event study. I think it even dramatically increases our desire for a post-event study, and let's assume we, we immunize 10,000 children in a week, in a large city, which is not a bad number, um, to, to suggest. It might be 100,000 or more but, let's say it was 10,000 children. Well, if we only got 10% of that population to enroll, we would have the most robust study of this problem ever done.

So, I, I think the, the challenge is to find the scientist willing to do the work to sort out what the study is, go through the processes, pre and post-event, and have them on the shelf ready to roll with IRB approvals and just have to dust them off a little bit but, this isn't easy but, it does take a federal commitment, at the level of money and manpower that that's quite substantial.

DR. MARSHALL: So, I'll just say briefly, I agree with Alan. And, I would think that it's important, uh, post-event to also think about compliance and sort of clinician behavior. If we go back to what we learned during H1N1 and what we know about seasonal influenza among pregnant women, um, the data or, I mean the trend is improving but it's rather dismal just to look at, you know, gynecologic practices and whether gynecologist, you know, obstetricians and gynecologists themselves are vaccinated. Whether their staff is vaccinated. And, whether they offer vaccine to their patients. Whether they promote it. So, I think that would be an important component of post-event research.

DR. GRADY: I wanted to ask Dr. Benjamin. Um, you said something, um, like we need a new research model that incorporates children. So, I wanted to ask if you could say more about that in two ways. One is do you think that the current model that we have that limits the amount of risk we allow children to take in research and justifies it in some narrow ways benefit to them or, you know, very narrow benefit to others, is that what we should change and, if so, how?

And, and second question or second part of that question, and anyone else who has an answer to this, I would love to hear it too, do you think there's a specific kind of framework that we should be thinking about, specifically, not, for AVA but for MCM research?

DR. BENJAMIN: Um, I, I think the framework that we're working on in terms of, of a risk that's slightly above, you know, um, minimal risk, um, is the right framework but, we don't, I don't think we even use that one very well. Um, I, I think we, we have artificially constrained that, um –

DR. GRADY: You mean interpreting it too narrowly?

DR. BENJAMIN: Interpreting it too, narrowly, probably. Um, um, you know, I, you know, one person's risk is not everyone's risk. Um, I do think that population health, there's a value, particularly with medical countermeasures of looking at the whole risk to a population.

Um, contagious disease is different from non-contagious disease. So, anthrax is a non-contagious disease but, what conversation would be having today if those letter had of gone to a school? We'd be having a very different conversation today. And, I think that's what I mean. I think the context on which we're thinking, um, when someone said during, you know, during, I guess, uh, Katrina, the failure of imagination. We haven't really imagined all of the kinds of permutations that could occur. Um, and because of that we've built our research models around, you know, kind of common things. Kind of the way we think about disease processes.

Um, but if somebody wanted to cause enormous terror, they could do so, um, in very, very simple ways. And, our response to that, I mean we know how parents are going to respond. We know how they're going to respond today. I don't want the vaccine. But, if my kid was exposed to this dust, they're going to respond quite differently. I can't predict what their response will be but, I can predict it will be different. There will be some that will want it. There will be some that will demand it. There will, you know, it depends.

Um, let's say that it occurred on, um, unknowingly, on a, on a scene of our first responders. They respond to an event, um, and then, they're secondarily exposed because we know that some of these, these, these bad guys and, um, um, do one event, and then, a secondary event is part of their response. Um, so they take something unknowingly home. They're going to respond quite differently, um, if they, if their family members, you know, are, are exposed. And, I don't think that our – that our models have caught up with that, um, in terms of that kind of thinking.

Um, they may be models that only get kicked in, in these unusual circumstances. Um, but if we don't ask those questions, now, um, we're not going to, you know, we're not going to be able to answer those question later. And, again, the way we all behave in an emergency is very, very different, um, then we, you know, then we behave in calm.

And, I think a lot of the, a lot of our thinking about this has got to be built into the research design. Um, in the consent forms, in the explanations that we give people. Um, they're not doing this because they're just simply trying to advance science. Um, they would be doing this because at the end, when all the studies are done, they're going to save lives, and not five lives, not ten lives, maybe millions of lives depending on the threat, depending on the agent, depending on the dispersal method. So that the scale up in terms of the risk to, to our society, to our population, um, can be enormous, you know, can be enormous. And, I think that's what makes this kind of research both pre-event and post-event so different than the classic, you know, study, strong research model, um, that we have.

I, again, I, as a, as a resident, I remember, um, a medical student as a resident. You know, I lived through the time when kids didn't survive therapy for leukemia. Um, and now, you know, we treat them and they're out playing the next day, after their chemotherapy. The same with breast cancer. You know, I remember women who died because we, well, you know, we poisoned them. We gave them really bad stuff. They didn't do well. And now, um, therapy has changed for both adults and kids, um, and we've, we've, we've, we've migrated our thinking about, about this, in a, in a variety of ways. Um, and I'm just encouraging us to do the same thing, you know, to our research enterprise around preparedness and medical countermeasures. Did I answer your question?

DR. GRADY: Sort of. I, I think one – I appreciate everything you just said. I just one question to ask to be clear about. So, I understand the consequences of not preparing and that that's a very serious, potentially very serious problem for all of us but, I guess the question still in my mind is what does that do today, if anything to change the way we think about exposing children to risk in the process of research? And, I guess, if I understood your first response to me, it would be maybe we thought, maybe we've been too conservative, and that we should allow children in research to accept a little bit more risk than we have in the past. Is that a fair restatement?

DR. BENJAMIN: That's fair, but only because of –

DR. GRADY: Of the big need.

DR. BENJAMIN: Of, the risk to them in the future is far greater today than it was, you know, five years ago, ten years ago.

DR. WAGNER: Are there others that wanted to – yes, Capt Maher.

CAPT MAHER: Thank you. I just wanted to add to that that we not lose sight of the fact that, when we're using the term medical countermeasure, we're not talking about all medical products that would be researched and developed. We're talking about a very specific subset of medical countermeasures that are intended for public health emergency responses to in some instances, when you're talking about biologic, radiologic, nuclear and chemical situations that you don't encounter every day, very dire situations that we hope we don't have to respond to.

So, the opportunity to study the medical countermeasures in the normal course of day-to-day uses would not be there. Um, and, and just to take advantage and to the earlier question about can it ethically be done post-exposure? I don't think the question should be can it ethically be done? I think we're in a situation where we have to figure out how are we going to ethically do it? Because for a lot of medical countermeasures that are in development for CBRN, that's the only time you're going to use them, and that's the only opportunity you're going to have to find out how well they're performing and whether or not they're safe and efficacious.

DR. GRADY: So, would you agree then that because of all that it justifies, um, asking children to accept more risk now in research?

CAPT MAHER: I think under the right circumstances in some situations, yes.

DR. FLEISCHMAN: Chris, I'll pick up on that. Uh, I think we have the right balance, right now. I think the rubric of the four permissible categories fits. It has some flexibility. Um, I would argue it would be a mistake to suggest to the public that we would place children at risk for these uncertain future events, at greater levels of risk. We have that flexibility within the present regulations, and learned groups that will be asked with public scrutiny to measure that balancing in real-time protocols with real-time events.

So, I would argue no, we don't need to increase risk to children but, we do need to increase research for children.

DR: SULMASY: Yeah, just, uh, in some ways related to that. I mean, we're often considering children to be vulnerable and a protected, and a protected class. And so, one of the ways of approaching the question is what are the circumstances under which we would relax those potentially, minimally relax those kinds of, uh, of protections.

Um, and one argument that one sometimes hears is that one of the conditions under which one might, provided the, you know, the risk is small enough, whatever that would mean, is that there'd be greater reason to do so, and do the research on a vulnerable class of individuals like children, if, the benefit that can be reaped from this research, accrues to members of the same class that makes them vulnerable in the first place, i.e., being children, and can only be studied by studying members of that class.

Um, now that seems to me to have some intuitive ring to it. Um, uh, uh, uh, we've had, uh, persons presenting to us who said we should – that makes no sense actually, if you look at it carefully, and that we should just do a risk/benefit analysis. And, I wondered what, uh, what the panelists here think about that.

DR. BENJAMIN: Well, clearly, if children are going to benefit from the research on children, I think it's an added plus. Um, I don't, I don't see the downside of them benefiting from that, assuming you do it, I don't see the downside of them benefiting from that.

DR. FLEISCHMAN: Dan, amen. Um, the 406, condition predicate is based in that. Um, I think we should con – you know, it would be terribly unfortunate if we sacrificed children for the sake of adults. I never mind sacrificing adults for the sake of children (laughter) but, it's, um – but, I, you know, I think that yes, they're vulnerable, and yes, they ought to be benefited by the results of the research.

CAPT MAHER: And to add to that, I think to the extent that, and this goes back to carefully thinking about what is it that we're asking? What is it that the study is, is looking at and trying to answer? That we also take a step back and we look at if there's any opportunity to study it elsewhere and extrapolate with confidence the information, which is something that we do today. That's what we would want to do.

Um, so to the extent that basic pediatric immunology research can be done to help inform and strengthen that extrapolation, um, that's something that should be contemplated, as well. Um, I would never agree to increasing risk of putting a child at risk for the benefit of adults. If the only way to gather the information, under the right, appropriate circumstances is in a pediatric population, then that needs to be considered and how would you do that in the most appropriate way?

DR. FARAHANY: I just wanted to follow-up on Dr. Fleischman's, um, comments in response saying that you think the existing regulations offer sufficient flexibility, uh, to address the questions that we have today. So, you know, one of the things we're contemplating, of course is, are the existing regulations sufficient? Are they sufficient, um, in the specificity? Are they sufficient in their breadth? Uh, and, of course, danger in over specifying is decreasing flexibility. Uh, and so, I'm wondering, if when you say, if you think that they are sufficient, do you think they are sufficient in specificity and do you think they are sufficient in breadth? Or, do you believe that there are pieces that are missing in the existing framework? And, do you have any advice for us as we think about that to ensure we maintain that flexibility?

DR. FLEISCHMAN: In the last decade, three learned groups have looked carefully, as much, as best I know at the present Subpart D regulations, and have all concluded that they ought not be changed, although there has been some debate in the community and many of, uh,

Professor Grady's colleagues have debated about definitions, um, minimal risk and what it means, etcetera, um, but the Institute of Medicine Review, the SACHARP Review, the Near Pack Review, all came to the same conclusions. Now, it is a few years later and we might want to do it again, um, but, I would argue that those regulations –

DR. WAGNER: May I, may I, jump in, uh, because I think the question, at least the aspect of the question that really got to me is not whether or not they should be changed because they are necessary but, are they also sufficient?

DR. FLEISCHMAN: Well, I believe they are sufficient. I, honestly do. I think it is how we are implementing these regulations. How IRB's are interpreting these regulations. How scientists are walking away from children's research rather than toward it. How we are underfunding research for children in this country. I mean there's a whole host of reasons that we aren't doing all the research we have to do in children but it isn't the regulations, in my opinion.

DR. WAGNER: So, you wouldn't add anything to those to address our particular issues?

DR. FLEISCHMAN: Nor, take them away.

DR. WAGNER: John, you are next.

DR. ARRAS: Yeah, uh, a comment and some questions. Uh, Alan, just to follow-up on this, this debate we're having here. Uh, I mean it does seem to me that, that the present regulations are – fall short of what we need, maybe not in terms of process. I think, you know, the 407 is a process, and we're engaging in it right now but, it's, uh, I think it falls short in terms of specificity. Okay? I mean, when, when 407, tells us to make decisions according to sound, ethical principles, the big question is what are you talking about? You know, what, what sound, ethical principles do you mean?

And, and, really, I think what we're talking about here is consideration for assent, consent and a respect for risk benefit, you know, ratio. Okay, so, I'm not – if you're arguing that the, that the present regulations are in good order to handle situations like this one, if you're arguing on a purely procedural basis, I would agree with you. But, if you're going to make a substantive argument, I would say that this notion, and this is, this is really where the rubber hits the road for us that sound, ethical principles need to be exfoliated, extrapolated, specified and that's the really hard slog that we're dealing with here. But that's just a comment. Did you want respond to that?

DR. WAGNER: Yes, let's let him respond.

DR. FLEISCHMAN: John, I look forward to reading this group's learned thoughts about those sound ethical principles. The question you need to ask after you write that is would you want that in the regulatory structure or would you like that in the materials that 407 committees and other learned groups in the future will read carefully, as they make these assessments? Having bounced around legislative, uh, worlds of public policy for a longtime, you might not get what you think you're going to get, when you try to codify in regulation those kinds of philosophical principles. Yet, those people doing the procedural approaches should take that learned information that you will add and they should be motivated to read that work.

DR. ARRAS: So, I don't yeah –- no, I agree with you that trying to put this kind of specificity into any kind of government wide regulation, I mean, the advice I would give is just pack a lunch. I mean that's going to be very difficult.

DR. WAGNER: But, Alan, you take John's point that – you argue very convincingly that it may be sufficient for what you would want to codify in regulation. And then for any specific application, uh, further insufficiencies of the guidance from the regulations need to be provided, and that

DR. ARRAS: Yeah, yeah, I mean, I'm okay with that.

DR. WAGNER: So, I think you're both

DR. ARRAS: I mean given the difficulty of, of, of, uh, specifying all of this at the level of the federal regulations, I agree with you that this could be viewed as helpful, supplementary frameworks for groups that will need to make these decisions. I don't think there's any –

DR. FLEISCHMAN: OHRP guidances, FDA or –

DR. ARRAS: Yeah, yeah.

DR. FLEISCHMAN: Whatever ways you put out your, your, uh, recommendations but, regulatory structures give us a lot, right now.

DR. ARRAS: Yeah, yeah, no. I think we're okay.

DR. WAGNER: John, I know you had a second one but, Dan wanted to jump in on this conversation.

DR. ARRAS: Yeah, sure.

DR. WAGNER: Real quick.

DR. SULMASY: Just wanted to say that this commission is already on record as endorsing regulatory parsimony, and I think that that –

DR. WAGNER: Good point.

DR. SULMASY: Settles the question between the two of you.
(Laughter)

DR. ARRAS: Yeah, yeah.

DR. WAGNER: Okay, Round Two.

DR. ARRAS: Okay, yeah, so getting to the questions. I've been – I've been, uh, chewing on this the last few days, lately. Uh, um, how do we – so, given the regulatory structure as it is from say 404 to 406, and then, we're now at 407. So, the question is how do we take the leap from 406, say to 407? Now, I, as I read it, there are three key predicates in 406. There's the, you know, subject of vital scientific importance that has to be satisfied. There has to be a group or a condition, a condition that the children have, uh, that links them up with a much larger group of children who are similarly afflicted. Um, and there has to be no more than a minor increase over minimal risk. Those are the three predicates within 406.

Now, my question to you is how do you propose we make the leap from 406 to 407? Because in 407, we don't have an analog of a condition other than just simply being a child, which I don't think they had in mind when they were drafting 406. I think, I think they were thinking of a disease of some sort. Okay? Um, and, so that's one impediment.

So, if I can formulate that into a question. Do you think that it's that morally salient to insist on a condition in 407, as opposed to simply belonging to a class of children? Okay? That's one question and that's not a loaded question because I think an, uh, uh, an answer can be given to that.

And, the other thing is the minimal risk. The minor increase over minimal risk. Okay? Here, I think is the biggest hurdle to going from 406 to 407, because if we're contemplating going beyond – if we're contemplating sticking with a level of minor increase over minimal risk, then, I think the transition from 406 to 407 is fairly smooth. Okay? But, if we're going to go beyond that, then it just becomes more difficult and I'd like to hear your comments on that.

DR. WAGNER: Sure, Alan.

DR. FLEISCHMAN: Um, I think you're right as you've described the differences between 406 and 407. I think this was done purposefully. The only problem I have is the vital

importance thing, which I mentioned. I think vital importance ought to be both in 406 and 407, and we ought, we – but, I don't know that you need to go to a regulatory change to get there but, I, but, I think that would be important to me.

The condition issue in 406, I think is important, um, and I believe in terms of the anthrax vaccine that we might have a minor increase over minimal risk as the risk level here but, you don't jump the condition, um, hurdle. And therefore, in 407, you actually eliminate condition and you say children as a class because you justify this based on the risk to all children of things like these kinds of public epidemics or other very serious events, which we're willing then to go to more than minor increase over minimal risk.

So, my three points. I wasn't as articulate as I would have liked to have been. Vital importance, I think we ought to do them both the same. Condition, stay in 406, which allows the local IRB to review something, minor increase over minimal risk. And, it has to be relevant to that child's group, peer group that he will volunteer to help others in the future who have the same disorder or disease. I think that's quite reasonable. But, in 407, we have children as a class and that's why we have a much more rigorous review process. We elevate it to the national level. We have convened an expert group, after an IRB at the local level has wanted to approve this but cannot. And, the third part, minor increase over minimal risk, I think was a brilliant idea for 406, and I would argue based on the balancing of the real risk to children in general, we might place specific individual children, at a little bit more than minor increase over minimal risk in the 407 process. And that would be very specific to the specific protocol, the specific disease, the specific risk.

DR. ARRAS: I guess, I, yeah that sounds reasonable to me. I, I, I guess, I would just like to get some concrete language as to what that extra thumb distance would look like.

(Laughter)

DR. ALLEN: In some ways my question is a follow-up to, um, this one, but it also harks back to an earlier part of the conversation because I was totally charmed by the response to the question, "Why would a reasonable parent do this?" It's because we want a model altruism. We want to teach altruism because we're community minded. We care about other people. All that was so – I almost was like so dazzled I couldn't even think beyond that but, um, but then, I began to wonder, okay, so, uh, we don't make our children join the army because it's, you know, going to be good for the community. We don't make our children give away their toys to be poor children because we don't – because it's good for the other children. We don't, we don't, um, ask our children to give up their breakfast because it might be – enable us to help other people. So, what is it about this particular intervention or this particular countermeasure that makes us so persuaded that a reasonable parent would, should, could do this? Um, and, I have no trouble understanding why a parent would give their self-destructively anxious or raging child Zoloft or Ritalin or Risperdal. I have no – so, an eight-year-old, no trouble, at all because the child has a condition. Right? But, why should a reasonable parent stop with its good for the

community and it models altruism. Why should they stop there? Why is that the place where the reasonable parent stops? Why don't they engage more with some of the concerns that we're engaging with? Go beyond questions about just giving to the community. I guess, I just want some more maybe harder reflection on why a reasonable parent would be willing to do this. Was I too passionate? (Laughter) Sorry.

CAPT MAHER: My thoughts, I think it really depends on what the perception of that reasonable parent is with regard to the risk to the child or the risk of this happening, and, um, whether or not in some cases, the child is going to receive something anyway. Um –

DR. ALLEN: Therapeutic misconception?

CAPT MAHER: Perhaps.

DR. ALLEN: Misunderstanding of risk?

CAPT MAHER: Perhaps or, or maybe a better understanding of the risk, if the -- I think a reasonable parent who truly believes that their child might be at risk for something may be more compelled to enroll their child in a trial like this with all the additional altruism behind it because they, they perhaps accept that there is a potential risk and that I need to help. That's the only thing I can think of in the way you framed the question for this particular type of topic, medical countermeasure research.

DR. ALLEN: So, this might be a context in which we really should honor the beliefs of parents about risk and about, uh, benefit, even if we don't necessarily agree with them. We, as leaders and policymakers. Yes?

CAPT MAHER: Yeah, I think so, and I think it goes back to understanding and, and, you know, really trying to, to tease through a lot of those assumptions that we've made and really understanding what it is that the public would do. What is acceptable to the public. What does the public want? What does a parent want before during and after an emergency?

DR. RASMUSSEN: Yes, I think some of it is depending on what level of risk you're thinking of. If it's a sore arm, feeling a little achy for a few days, I think I would allow my children to, you know, they're of the age that they can make their decision themselves but, I would support their decision. I would offer that they have participated in medical research before. Medical research that I thought was minimal risk but, they wanted to be part of the scientific process. They knew they would be helping other children. They felt that was an important thing, and, and it really wasn't encouraged by me. Now, I do think my son was a little motivated by the money because he did ask was it going to be cash. So, uh, you know, but, you

know, it was really a time sort of thing. It was minimal risk but, I think, I think some of it is that, is thinking of what the level of risk we're anticipating here. If you told me it was a risk of him dropping dead, I'd say, "No, thank you. Forget it." I'm not doing anything at that level of risk. I guess, I think that's probably not the level of risk we're talking about but –

DR. FLEISCHMAN: It was passionate, Anita, but I appreciate it. Um, at the Episcopal Church in Garrison, New York, yesterday, the youth group announced that they were collecting money and they were going to Staten Island on Tuesday and Queens on the following Saturday in New York, um, to give toys and money and food to victims of the hurricane. Um, they announced it. They decided this was the thing to do, and their, uh, Sunday School teacher had organized these events with other Episcopal churches in the communities that had been most affected.

I was quite, uh, taken by that. I happened to be there that day, not that it's my church. Um, and, uh, yes altruism does ring high in many communities and it's good and we should, uh, I think applaud it. Um, our job though is to develop the threshold, the level of risk above which we would not let altruistic parents place their children at risk, um, and we – that level, that, that threshold is very important. And then, we should not expect that all parents will place their children at risk but, we should allow those who would do it, and those who would share that responsibility of decision making with their children, we should have an assent approach that gives that child all of the information he or she needs in order to make that decision and respect that judgment if they refuse or are reluctant.

DR. ALLEN: So, is the -- so, is the answer to the question, "Why would a reasonable parent do this?" Essentially because it's not that risky? Is that the answer?

DR. FLEISCHMAN: No, no, that it -- it has some level of risk but that learned groups have said it's not so great.

DR. ALLEN: Not that risky and I'm an altruist.

DR. FLEISCHMAN: Well, we can put it that way.

DR. ALLEN: Yeah, okay that's good.

DR. MARSHALL: And, how does it fit into my worldview about the health of my child and the future health of my child and my obligation, my duty as a parent to my child's health and continued health. And so, that risk assessment that is independent, you know, all of my children have four legs. I have to confess. I don't have children, you know, human children, um, so, this is kind of theoretical from my perspective, although I'm glad it has been tested in animals because I have, uh, I have a number of them. Um, but I, but I think it has to do perhaps with

lived experience. Uh, and it has to do with my concept as a parent of my duty or obligation to my child. My child's current health and my child's, you know, future health, especially given the lethality of anthrax. I think it's important, you know that's 75% mortality is an important number. Even, you know, sort of given a low, a low risk. Right? If there are – It's high lethality, you don't need, you know, huge numbers of children to make it a question of vital importance.

CAPT MAHER: If I could add something very, very quickly, too. It, it struck me that as we're answering this question, we really need to be very careful because we're talking about two levels of risk. There's the risk of the threat and how real the risk of the threat may be perceived by a parent and that's from the perspective I was answering the question. But, as I'm hearing my colleagues, there's the risk perception of putting myself at risk by participating in the trial. So, there's – we have to be very careful because you have different, um, you have interplay with different risk assessments going on in, in answering that question.

DR. HAUSER: So, I think Dr. Rasmussen, when you were responding as a parent that, uh, I'm sure that struck many of us around the table because we are as we're trying to grapple with this idea of what is minimum, what is a minor increase over minimal risk. We've really also have two types of categories. One is the discomfort reversible complication, and the other that in some of the written material we are, uh, we see, um, added to this category are irreversible complications that are extraordinarily rare in a population base, uh, that may be minor but certainly not to the parent whose child experiences this. And, in the material we received radiation exposure is a very good one for a child where one has a certain theoretical risk of a, of a small amount of radiation exposure, and the rare one to million vaccine complication rate that is there for many vaccines would be another example.

So, somehow figuring out the, um, how we respond to the more common but reversible, uh, side effects and these very rare events that may not be reversible, I think is important.

DR. ARRAS: Yes because, yes, I mean, we get lots of mail. (Laughter) We get, we get, you know, lots of comments, lots of comments come in, uh, and, uh, I'm in no position to, you know, uh, uh, judge the accuracy of a lot of the medical comments that are made by various people that we get but, you know, I'm looking at one of them here, Stephen, you know, which talks about how the new labeling of this vaccine provided a higher systemic adverse event rate of 5% to 35%, then the prior label of .2%. And, it also noted without using the term Gulf War that illnesses meeting the CDC's case definition of Gulf War illness had been reported.

Now, you know, I mean, I know that it's difficult to establish a cause and effect relationship from self-reported incidents of this sort but, but, letters like this trouble me, you know, because I, I mean it's one thing to talk about minimal risk or a slight increase over minimal risk, and, and there we're thinking, well we had, uh, uh, someone give testimony from Hopkins who said this is just basically as, as, uh, worrisome as your average flu shot. You

know, now if that's the case then, I think we're in good shape here. You know? Um, on the other side of the spectrum, nobody's going to disagree that death, you know, death or serious hospitalization is going to be a risk that we would, that we would say a prudent parent would permit. But, I'm still trying to get a handle on those risks that are on the other – that are in-between those two, you know, and how we're supposed to come to a conclusion about this, when we've got conflicting evidence about short-term risk and long-term risks.

DR. MARSHALL: I'm not sure this is apt but, I, I can remember some years ago, reviewing, reviewing a study. It may have been a 407 panel. My memory doesn't serve. But, I do remember that in the, the, the informed consent document for the parent, the level of risk was described as a reasonable, what a reasonable parent would allow his child to play in the street. And, you know, that was appalling but that was in a protocol. So, that's why the funny, that's why the –

DR: ARRAS: The same as the parent letting the child play in the street?

DR. MARSHALL: Right and what reasonable parent – I mean, it begs the question, so, what reasonable parent is going to allow his or her child to play in the street? One would hope no reasonable parent would do that.

DR. ARRAS: My response to that is every parent on my block when I was growing up. (Laughter)

DR. MARSHALL: To play in traffic? I'm sorry, it was probably to play in traffic but –

DR. ARRAS: That's where we played.

DR. MARSHALL: Yeah, sorry that probably wasn't apt.

DR. FLEISCHMAN: Two comments, John. Um, one the plural of anecdote is not data, and I think you ought to mine the data that exists in the six million doses that have been given and mine it carefully. And then, have some of our epidemiologists talk to you about what that suggests and what has been attributed to the vaccine versus what might be attributed to the vaccine or what is extraordinarily unlikely to be attributed to the vaccine. And, I, I think that's part of the protocol that I'd love to see in which in it, the scientist have to embed that justification because they've reviewed all those data.

If we find the data lacking in the published data, then I think this group has every right to go to the department of defense and say, "What you got?" Because most of those people were in the department of defense's supervisor capacity.

Um, but there are data. So, we could, at least look at those in order to, to make some suggestions. I mean, everybody gets letters about various things and anecdotes are, are that and I would agree with you, if those were, in fact, substantiated data that our soldiers were placed at that kind of risk and had this problem. Then, I don't think we would wish our children to be placed at that risk.

DR. ATKINSON: I have really two, two issues. One, um, other, other panels we've listened to there's been some discussion about whether to actually exclude the military and first responders from allowing themselves to volunteer their children because of the coercion factor but, also just because they've already done enough, if you will. So, I'm interested in what you think about that.

But, then, I'm also interested in the issue of compensation. In clinical trials, there's no recommendation that, that patients with adverse effects should get compensated or even treated necessarily for whatever the complication is. Would you think – this is a different case, and if you're having children in a study for an altruistic reason for the good of everybody, should there be some level of compensation promised in that case?

MR. LOCKWOOD: So, related to the issue of first responders. Um, I actually look at it a little differently. They have done a lot, not they've done enough. And, I look at it in the sense of this is the one thing that we may be able to provide to the first responders as a, um, method to protect their families. Um, as to compensation, I'm not going to answer that but, um, I just look at the fact that that is a viable, um, tool to provide to them. So, I don't look at it as enough. It's a way that we can work to assist them.

CAPT MAHER: I think it goes back to really going into the community of first responders and DOD and asking them the question. We're making assumptions about, you know, there's assumptions on the one side that they wouldn't. There's assumptions that they would be more willing. There's assumptions that they would – there's a coercion fact. And, I think we need to really go back and look at those assumptions and, and go to the source and find out what the reality is.

And, with regard to the compensation, this is a very personal response. This is not, is not the agency response or anything like that but, a very personal response. As a nurse and as a mom, if I were to put my child in a study. I think there should be. I think if somebody is injured in the course of the study, then they should be taken care of, all the way through that injury. They wouldn't have been injured otherwise.

DR. MARSHALL: I agree about the compensation for research injury and sort of have maintained that for a longtime. It may involve TORT reform, um, but it seems to me that it should be factored in upfront as part of the, as a price, as part of the price of doing research. And, uh –

DR. WAGNER: If there -- staff has allowed us to go on for another 15 minutes, if we care to but, I kind of think we've wrung this one out and I'll suggest we -- I'll suggest that, uh, we reconvene at 3:00, but not until we first thank all of you very much.

(Applause)